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Date: February 18, 2000

Docket No.: 2801-136P

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

This is a Request for filing a ☒ continuation ☐ divisional application under 37 C.F.R. § 1.53(b) of pending prior Application No. 08/945,141 filed on October 14, 1997, the entire contents of which are hereby incorporated by reference, by

Ignatius Loy Britto

for

METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

1. ☒ Enclosed is an application consisting of specification, claims, declaration and drawings/photographs (if applicable).

2. ☒ The filing fee has been calculated as follows:

			LARGE ENTITY	SMALL ENTITY
	BASIC FEE		$690.00	$345.00
	NUMBER FILED	NUMBER EXTRA	RATE FEE	RATE FEE
TOTAL CLAIMS	30-20 =	10	x 18 =$180.00	x 9 = $0.00
INDEPENDENT CLAIMS	2-3 =	0	x 78 = $0.00	x 39 = $0.00
☐ MULTIPLE DEPENDENT CLAIMS PRESENTED			+ $260.00	+ $130.00
		TOTAL	$870.00	$0.00

3. ☑ A check in the amount of **$870.00** to cover the filing fee and recording fee (if applicable) is enclosed.

4. ☐ Please charge Deposit Account No. 02-2448 in the amount of $0.00. A triplicate copy of this request is enclosed.

5. Amend the specification by inserting before the first line thereof the following:

   a. ☐ --This application is a ☐ continuation ☐ divisional of co-pending Application No. 08/945,141, filed on, the entire contents of which are hereby incorporated by reference.--

   b. ☐ --This application is a ☐ continuation ☐ divisional of co-pending Application No. 08/945,141, filed on. Application No. 08/945,141 is the national phase of PCT International Application No. PCT/_____/_____ filed on _____ under 35 U.S.C. § 371. The entire contents of each of the above-identified applications are hereby incorporated by reference.--

6. ☐ Transfer the drawings/photographs from the prior application to this application and abandon said prior application as of the filing date accorded this application. A duplicate copy of this request is enclosed for filing in the prior application file.

7. ☐ Enclosed is/are _____ (____) sheet(s) of drawings and/or photographs.

8. ☐ A statement claiming small entity status was filed in prior Application No. 08/945,141 on _____. See the attached copy of the statement claiming small entity status.

9. ☒ The prior application is assigned to GlaxoWellcome, Inc.

10. √☒ A Preliminary Amendment is enclosed.

11a. ☐ Priority of Application No(s). _____ filed in _____ on _____ is/are claimed under 35 U.S.C. § 119. See attached copy of the Letter claiming priority filed in the prior application on _____.

11b. ☐ Priority of International Appln. filed on under the Patent Cooperation Treaty and Application No. filed in on under 35 U.S.C. § 119 and/or 35 U.S.C. § 120 are hereby reclaimed.

12. √☒ An Information Disclosure Statement and PTO-1449 form(s) are attached hereto for the Examiner's consideration.

13. ☒ Address all future communications to:

BIRCH, STEWART, KOLASCH & BIRCH, LLP
P.O. Box 747
Falls Church, VA 22040-0747
Telephone: (703) 205-8000
or
Customer No. 2292

14. ☐ An extension of time for _____( ) month(s) until has been submitted in parent Application No. 08/945,141 in order to establish co-pendency with the present application.

15. ☐ Also enclosed herewith is the following:

_____

_____

_____

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Gerald M. Murphy, Jr., #28,977

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GMM/MWM/las/cc
2801-136P

Attachments: Check in the amount of $852.00
Preliminary Amendment
Specification
Information Disclosure Statement & PTO Form-1449
Copy of Executed Declaration

(Rev. 01/08/2000)

PATENT
Docket No. 2801-136P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Ignatius Loy BRITTO

APPLN. NO.: NEW GROUP: Unassigned

FILED: February 18, 2000 EXAMINER: Unassigned

FOR: METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents February 18, 2000
Washington, DC 20231

Sir:

The following preliminary amendments and remarks are respectfully submitted in connection with the above-identified application.

In the Specification:

Please amend the specification as follows.

Page 1

On the first line of the specification, after the title, insert --This application is a 37 C.F.R. § 1.53(b) continuation of copending U.S. Application No. 08/945,141, which was filed pursuant to 35 U.S.C. § 371 as a United States National Phase Application of International Application No. PCT/US96/05009 filed April 11, 1996, which claims priority from U.S. Application 08/422,280, filed April 14, 1995, abandoned. The entire contents of each of the above-identified applications are hereby incorporated by reference.--

Page 5

Line 10, change "valve then" to --valve. Then--

Page 6

Line 18, change "(PTFE)" to --(TFE; which is used to prepare polytetrafluoroethylene (PTFE))--; change "fluorinated" to --perfluorinated--; change "(FEP)" to --(FEP; which is perfluorinated ethylene propylene copolymer, which is a copolymer of TFE and hexafluoropropylene (HFP))--

Line 19, change "perfluoroalkoxyalkane (PFA)" to --perfluoroalkoxyalkylene (PFA; which is a perfluoroalkoxy fluorocarbon polymer which is prepared using a perfluoroalkyl vinyl ether monomer)--; change "(ETFE)" to --(ETFE; ethylene-tetrafluoroethylene copolymer)--

Line 20, change "vinyldienefluoride (PVDF)" to --vinylidene fluoride (PVDF; polyvinylidene fluoride)--; and after "chlorinated ethylene tetrafluoroethylene" insert --(a copolymer made by copolymerizing chlorinated ethylene and tetrafluoroethylene)--

Page 7

Line 2, after "Hostaflon®" insert --(a copolymer prepared by copolymerizing TFE and perfluoropropyl vinyl ether)--

Line 3, after "PFA DuPont 857-200" insert --(a copolymer prepared by copolymerizing TFE and perfluoropropyl vinyl ether)--

Page 8

Line 27, change "proper" to --primer--

In the Claims:

Please cancel claims 1-21 without prejudice or disclaimer to the subject matter contained therein.

Please add the following claims.

--22. A metered dose inhaler ("MDI"), comprising:

a can having part or all of its internal surfaces coated with a polymer blend comprising one or more fluorocarbon polymers, in combination with one or more non-fluorocarbon polymers;

a crimped cap covering the mouth of the can; and

a drug metering valve situated on the cap.--

--23. The MDI according to claim 22, further comprising an inhalation medicament formulation, comprising a medicament formulated with a fluorocarbon propellant.--

--24. The MDI according to claim 23, wherein said medicament formulation further comprises a surfactant.--

--25. The MDI according to claim 23, wherein said medicament formulation further comprises a polar solvent.--

--26. The MDI according to claim 23, wherein said medicament formulation comprises 0.01 to 5 % w/w based on the weight of propellant of a polar cosolvent.--

--27. The MDI according to claim 25, wherein the polar solvent is ethanol.--

--28. The MDI according to claim 22, further containing a medicament formulated with a fluorocarbon propellant and 0.01 to 5 % w/w based on the propellant of a polar cosolvent, which formulation is substantially free of surfactant.--

--29. The MDI according to claim 23, wherein the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof.--

--30. The MDI according to claim 29, wherein the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane.--

--31. The MDI according to claim 22, wherein said can is made of metal and wherein part or all of the internal metallic surfaces are coated.--

--32. The MDI according to claim 31, wherein the metal is aluminum or an alloy thereof.--

--33. The MDI according to claim 22, wherein said one or more fluorocarbon polymers is a perfluorocarbon polymer.--

--34. The MDI according to claim 33, wherein said one or more fluorocarbon polymers is selected from the group consisting of polytetrafluoroethylene, perfluoroalkoxyalkylene, perfluorinated ethylene propylene copolymer and a mixture thereof.--

--35. The MDI according to claim 22, wherein said one or more fluorocarbon polymers is blended with a non-fluorocarbon polymer selected from the group consisting of polyamideimide and polyethersulfone.--

--36. The MDI according to claim 22, wherein said comprises a substantially ellipsoidal base.

--37. The MDI according to claim 22, wherein said fluorocarbon polymer comprises monomeric units made from one or more monomers selected from the group consisting of tetrafluoroethylene, hexafluoropropylene, perfluoroalkoxyalkylene, and vinylidene fluoride.--

--38. The MDI according to claim 22, wherein said non-fluorinated polymer is selected from the group consisting of a polyamide, a polyimide, a polyamideimide, a polyethersulfone, a polyphenylene sulfide and an amine-formaldehyde thermosetting resin.--

--39. The MDI according to claim 38, wherein said non-fluorinated polymer is a polyethersulfone.--

--40. The MDI according to claim 34, wherein said fluorinated polymer is polytetrafluoroethylene.--

--41. The MDI according to claim 22, wherein said blend comprises polytetrafluoroethylene and polyethersulfone.--

--42. The MDI according to claim 22, wherein said blend consists of polytetrafluoroethylene and polyethersulfone.--

--43. The MDI according to claim 22, wherein said fluorinated polymer is made from monomeric units comprising perfluoroalkoxyalkylene.--

--44. The MDI according to claim 22, wherein said fluorinated polymer is made from monomeric units comprising perfluorinated ethylene propylene.--

--45. The MDI according to claim 22, wherein the thickness of said coating is 1 μm to 1 mm.--

--46. The MDI according to claim 22, wherein the thickness of said coating is 1 μm to 100 μm.--

--47. The MDI according to claim 22, wherein the thickness of said coating is 1 μm to 25 μm.--

--48. The MDI according to claim 31, wherein said coating is applied to said internal surface of a preformed can.--

--49. The MDI according to claim 31, wherein said coating is applied by spray coating said polymer blend.--

--50. The MDI according to claim 31, wherein said coating is applied by spray coating said polymer blend on the internal metallic surface of said can and curing said coating after it is sprayed.--

--51. A metered dose inhaler can, comprising:

a metered dose inhaler can having part or all of its internal surfaces coated with a polymer blend comprising one or more fluorocarbon polymers, in combination with one or more non-fluorocarbon polymers.--

REMARKS

The present application has been filed to claim subject matter disclosed in the parent application but not specifically covered by the allowed claims in the parent application. For example, new claim 22 has does not have the language concerning the "intended use" of the metered dose inhaler (MDI), e.g., "for dispensing . . .."

Dependent claim 23 and other claims which recite that the MDI further contains a medicament and a propellant, cover this feature.

The above amendments to the specification are the same ones made in the parent application. They have been made in order to correct typographical errors on page 6 of the specification, e.g., "vinyldiene" to "vinylidene" and at page 8, line 27. The specification has also been amended to provide definitions for the various abbreviations and to identify the "monomers" and/or "monomeric units" that some of the polymers are made from.

Support for new claim 22 can be found page 6, lines 15-32 and page 7, lines 20-30. Support for new claims 23 and 28 can be found on page 4, lines, 12-33 and page 5, lines 6-14 and page 3, lines 19-24. Support for new claims 37 and 38 can be found on page 6, lines 18-20 and page 6, lines 25-28, respectively. The support for new claims 45-47 can be found on page 7, lines 5-7. The support for new claims 48 and 49 can be found on page 9, lines 7-9. All other new claims are rewritten from the original claims so that dependencies are easier to follow.

If there are any minor matters precluding allowance of the application which may be resolved by a telephone discussion, the Examiner is respectfully requested to contact Mark W. Milstead (Reg. No. P-45,825) at (703) 205-8000.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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2801-136P

METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

BACKGROUND OF THE INVENTION

Drugs for treating respiratory and nasal disorders are frequently administered in aerosol formulations through the mouth or nose. One widely used method for dispensing such aerosol drug formulations involves making a suspension formulation of the drug as a finely divided powder in a liquefied gas known as a propellant. The suspension is stored in a sealed container capable of withstanding the pressure required to maintain the propellant as a liquid. The suspension is dispersed by activation of a dose metering valve affixed to the container.

A metering valve may be designed to consistently release a fixed, predetermined mass of the drug formulation upon each activation. As the suspension is forced from the container through the dose metering valve by the high vapor pressure of the propellant, the propellant rapidly vaporizes leaving a fast moving cloud of very fine particles of the drug formulation. This cloud of particles is directed into the nose or mouth of the patient by a channelling device such as a cylinder or open ended cone. Concurrently with the activation of the aerosol dose metering valve, the patient inhales the drug particles into the lungs or nasal cavity. Systems of dispensing drugs in this way are known as "metered dose inhalers" (MDI's). See Peter Byron, *Respiratory Drug Delivery*, CRC Press, Boca Raton, FL (1990) for a general background on this form of therapy.

Patients often rely on medication delivered by MDI's for rapid treatment of respiratory disorders which are debilitating and in some cases, even life threatening. Therefore, it is essential that the prescribed dose of aerosol medication delivered to the patient consistently meet the specifications claimed by the manufacturer and comply with the requirements of the FDA and other

regulatory authorities. That is, every dose in the can must be the same within close tolerances.

Some aerosol drugs tend to adhere to the inner surfaces, i.e., walls of the can, valves, and caps, of the MDI. This can lead to the patient getting significantly less than the prescribed amount of drug upon each activation of the MDI. The problem is particularly acute with hydrofluoroalkane (also known as simply "fluorocarbon" propellant systems, e.g., P134a and P227, under development in recent years to replace chlorofluorocarbons such as P11, P114, and P12.

We have found that coating the interior can surfaces of MDI's with a fluorocarbon polymer significantly reduces or essentially eliminates the problem of drug adhesion or deposition on the can walls and thus ensures consistent delivery of medication in aerosol form from the MDI.

SUMMARY OF THE INVENTION

A metered dose inhaler having part or all of its internal metallic surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising beclomethasone dipropionate or a physiologically acceptable solvate thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

DETAILED DESCRIPTION OF THE INVENTION

The term "metered dose inhaler" or "MDI" means a unit comprising a can, a crimped cap covering the mouth of the can, and a drug metering valve situated in the cap , while the term "MDI system" also includes a suitable channelling device. The terms "MDI can" means the container without the cap and valve. The term "drug metering valve" or "MDI valve" refers to a valve and its associated mechanisms which delivers a predetermined amount of drug formulation from an MDI upon each activation. The channelling device may

comprise, for example, an actuating device for the valve and a cylindrical or cone-like passage through which medicament may be delivered from the filled MDI can via the MDI valve to the nose or mouth of a patient, e.g. a mouthpiece actuator. The relation of the parts of a typical MDI is illustrated in US Patent 5,261,538 incorporated herein by reference.

U.S. Patent No.3,312,590, incorporated herein by reference, teaches an antiinflammatory steroid compound know by the chemical name 9-chloro-1 1D, 17, 21-trihydroxy-16fi-methylprergna-1,4-diene-3, 20-dione 17, 21-dipropionate and the generic name "beclomethasone dipropionate". Beclomethasone dipropionate in aerosol form, has been accepted by the medical community as useful in the treatment of asthma and is marketed under the trademarks "Beclovent", "Becotide", and "Beconase".

The term "drug formulation" means beclomethasone dipropionate (or a physiologically acceptable solvate thereof) optionally in combination with one or more other pharmacologically active agents such as other antiinflammatory agents, analgesic agents or other respiratory drugs and optionally containing one or more excipients. The term "excipients" as used herein mean chemical agents having little or no pharmacological activity (for the quantities used) but which enhance the drug formulation or the performance of the MDI system. For example, excipients include but are not limited to surfactants, preservatives, flavorings, antioxidants, antiaggregating agents, and cosolvents, e.g., ethanol and diethyl ether.

Suitable surfactants are generally known in the art, for example, those surfactants disclosed in European Patent Application No. 0327777. The amount of surfactant employed is desirable in the range of 0.0001% to 50% weight to weight ratio relative to the drug, in particular, 0.05 to 5% weight to weight ratio. A particularly useful- surfactant is 1,2-di[7-(F-hexyl) hexanoyl]-glycero-3-phospho-N,N,N-trimethylethanolamine also know as 3, 5, 9-trioxa-4-phosphadocosan-1-aminium, 17, 17, 18,18,19, 19, 20, 20, 21, 21, 22, 22, 22-tridecafluoro-7-[(8, 8, 9, 9,10, 10, 11, 11, 12, 12, 13, 13, 13-tridecafluoro-1-oxotridecyl)oxy]-4-hydroxy-N, N, N-trimethyl-10-oxo-, inner salt,.4-oxide.

A polar cosolvent such as C_{2-6} aliphatic alcohols and polyols eg ethanol, isopropanol and propylene glycol, and preferably ethanol, may be included in the drug formulation in the desired amount, either as the only excipient or in addition to other excipients such as surfactants. Suitably, the drug formulation may contain 0.01 to 5% w/w based on the propellant of a polar cosolvent eg ethanol, preferably 0.1 to 5% w/w e.g. 0.1 to 1% w/w.

It will be appreciated by those skilled in the art that the drug formulation for use in the invention may, if desired, contain beclomethasone dipropionate (or a physiologically acceptable solvate thereof) in combination with one or more other pharmacologically active agents. Such medicaments may be selected from any suitable drug useful in inhalation therapy. Appropriate medicaments may thus be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; antiinfectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. fluticasone (e.g. the propionate), flunisolide, budesonide, tipredane or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. salbutamol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol, orciprenaline, or (-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Particularly preferred drug formulations contain beclomethasone dipropionate (or a physiologically acceptable solvate thereof) in combination with a bronchodilator such as salbutamol (e.g. as the free base or the sulphate salt) or salmeterol (e.g. as the xinafoate salt).

"Propellants" used herein mean pharmacologically inert liquids with boiling points from about room temperature (25°C) to about -25°C which singly or in combination exert a high vapor pressure at room temperature. Upon activation of the MDI system, the high vapor pressure of the propellant in the MDI forces a metered amount of drug formulation out through the metering valve then the propellant very rapidly vaporizes dispersing the drug particles. The propellants used in the present invention are low boiling fluorocarbons; in particular, 1,1,1,2-tetrafluoroethane also known as "propellant 134a" or "P134a" and 1,1,1,2,3,3,3-heptafluoropropane also know as "propellant 227" or "P 227".

Drug formulations for use in the invention may be free or substantially free of formulation excipients e.g. surfactants and cosolvents etc. Such drug formulations are advantageous since they may be substantially taste and odour free, less irritant and less toxic than excipient-containing formulations. Thus, a preferred drug formulation consists essentially of beclomethasone dipropionate (or a physiologically acceptable solvate thereof), optionally in combination with one or more other pharmacologically active agents particularly salbutamol (or a physiologically acceptable salt thereof), and a fluorocarbon propellant. Preferred propellants are 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof, and especially 1,1,1,2-tetrafluoroethane.

Most often the MDI can and cap are made of aluminum or an alloy of aluminum, although other metals not affected by the drug formulation, such as stainless steel, an alloy of copper, or tin plate, may be used. An MDI can may also be fabricated from glass or plastic. Preferably, however, the MDI cans employed in the present invention are made of aluminium or an alloy thereof. Advantageously, strengthened aluminium or aluminum alloy MDI cans may be employed. Such strengthened MDI cans are capable of withstanding particularly stressful coating and curing conditions, e.g. particularly high temperatures, which

may be required for certain fluorocarbon polymers. Strengthened MDI cans which have a reduced tendency to malform under high temperatures include MDI cans comprising side walls and a base of increased thickness and MDI cans comprising a substantially ellipsoidal base (which increases the angle between the side walls and the base of the can), rather than the hemispherical base of standard MDI cans. MDI cans having an ellipsoidal base offer the further advantage of facilitating the coating process.

The drug metering valve consists of parts usually made of stainless steel, a pharmacologically inert and propellant resistant polymer, such as acetal, polyamide (e.g., Nylon®), polycarbonate, polyester, fluorocarbon polymer (e.g., Teflon®) or a combination of these materials. Additionally, seals and "O" rings of various materials (e.g., nitrile rubbers, polyurethane, acetyl resin, fluorocarbon polymers), or other elastomeric materials are employed in and around the valve.

Fluorocarbon polymers for use in the invention include fluorocarbon polymers which are made of multiples of one or more of the following monomeric units: tetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP), perfluoroalkoxyalkane (PFA), ethylene tetrafluoroethylene (ETFE), vinyldienefluoride (PVDF), and chlorinated ethylene tetrafluoroethylene. Fluorinated polymers which have a relatively high ratio of fluorine to carbon, such as perfluorocarbon polymers e.g. PTFE, PFA, and FEP, are preferred.

The fluorinated polymer may be blended with non-fluorinated polymers such as polyamides, polyimides, polyethersulfones, polyphenylene sulfides and amine-formaldehyde thermosetting resins. These added polymers improve adhesion of the polymer coating to the can walls. Preferred polymer blends are PTFE/FEP/polyamideimide, PTFE/polyethersulphone (PES) and FEP-benzoguanamine.

Particularly preferred coatings are pure PFA, FEP and blends of PTFE and polyethersulphone (PES).

Fluorocarbon polymers are marketed under trademarks such as Teflon®, Tefzel®, Halar® , Hostaflon®, Polyflon® and Neoflon®. Grades of polymer include FEP DuPont 856-200, PFA DuPont 857-200, PTFE-PES DuPont 3200-100, PTFE-FEP-polyamideimide DuPont 856P23485, FEP powder DuPont 532 and PFA Hoechst 6900n. The coating thickness is in the range of about 1μm to about 1mm. Suitably the coating thickness is in the range of about 1μm to about 100μm, e.g. 1μm to 25μm. Coatings may be applied in one or more coats.

Preferably the fluorocarbon polymers for use in the invention are coated onto MDI cans made of metal, especially MDI cans made of aluminium or an alloy thereof.

The particle size of the particular (e.g., micronised) drug should be such as to permit inhalation of substantially all the drug into the lungs upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than microns, and, in particular, in the range of 1-10 microns, e.g., 1-5 microns.

The final aerosol formulation desirably contains 0.005-10% weight to weight ratio, in particular 0.005-5% weight to weight ratio, especially 0.01-1.0% weight to weight ratio, of drug relative to the total weight of the formulation.

A further aspect of the present invention is a metered dose inhaler having part or all of its internal metallic surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more fluorocarbon polymers, for dispersing an inhalation drug formulation comprising beclomethasone dipropionate and a fluorocarbon propellant optionally in combination with one or more other pharmacologically active agents and one or more excipients.

A particular formulation for use in the metered dose inhaler of the present invention comprises:

(a) beclomethasone dipropionate monohydrate, the particle size of substantially all the monohydrate being less than 20 microns;

(b) at least 0.015% by weight of the formulation of water in addition to the water of crystallization associated with said monohydrate; and

(c) a fluorocarbon propellant.

Such aerosol formulations desirably contain at least 0.015% (e.g., 0.015 to 0.1%) by weight of the formulation of water (excluding the water of crystallization associated with the beclomethasone dipropionate monohydrate), preferably at least 0.02%, for example 0.025% by weight or more of added water. Preferred formulations according to the invention contain at least 0.026%, for example 0.026 to 0.08% by weight of water, in addition to the water of crystallization associated with the beclomethasone dipropionate monohydrate. Optionally, a cosolvent such as ethanol may be included in the formulation in the desired amount. Suitably, the formulation may contain 0.05 to 3.0% w/w based on the propellant of a polar cosolvent such as ethanol. Preferably the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof, and especially 1,1,1,2-tetrafluoroethane.

Further drug formulations for use in the invention are free or substantially free of surfactants. Thus, a further formulation comprises or consists essentially of beclomethasone dipropionate or a physiologically acceptable solvate thereof, optionally in combination with one or more other pharmacologically active agents, a fluorocarbon propellant and 0.01 to 0.05% w/w based on the propellant of a polar cosolvent such as ethanol, which formulation is free of surfactant. Preferably the propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane, although mixtures thereof may also be used.

A particular aspect of the present invention is an MDI having part or essentially all of its internal surfaces e.g. metallic surfaces coated with PFA or FEP, or blended fluoropolymer resin systems such as PTFE-PES with or without a proper coat of polyamideimide or polyethersulfone for dispersing a drug formulation as defined hereinabove. Preferably the MDI can is made of aluminum or an alloy thereof.

The MDI can may be coated by the means known in the art of metal coating. For example, a metal, such as aluminum or stainless steel, may be precoated as coil stock and cured before being stamped or drawn into the can shape. This method is well is suited to high volume production for two reasons. First, the art of

coating coil stock is well developed and several manufacturers can custom coat metal coil stock to high standards of uniformity and in a wide range of thicknesses. Second, the precoated stock can be stamped or drawn at high speeds and precision by essentially the same methods used to draw or stamp uncoated stock.

Other techniques for obtaining coated cans is by electrostatic dry powder coating or by spraying preformed MDI cans inside with formulations of the coating fluorinated polymer/polymer blend and then curing. The preformed MDI cans may also be dipped in the fluorocarbon polymer/polymer blend coating formulation and cured, thus becoming coated on the inside and out. The fluorocarbon polymer/polymer blend formulation may also be poured inside the MDI cans then drained out leaving the insides with the polymer coat. Conveniently, for ease of manufacture, preformed MDI cans are spray-coated with the fluorinated polymer/polymer blend.

The fluorocarbon polymer/polymer blend may also be formed in situ at the can walls using plasma polymerization of the fluorocarbon monomers. Fluorocarbon polymer film may be blown inside the MDI cans to form bags. A variety of fluorocarbon polymers such as ETFE, FEP, and PTFE are available as film stock.

The appropriate curing temperature is dependent on the fluorocarbon polymer/polymer blend chosen for the coating and the coating method employed. However, for coil coating and spray coating temperatures in excess of the melting point of the polymer are typically required, for example, about 50° C above the melting point for up to about 20 minutes such as about 5 to 10 minutes eg about 8 minutes or as required. For the above named preferred and particularly preferred fluorocarbon polymer/polymer blends curing temperatures in the range of about 300°C to about 400°C, e.g. about 350°C to 380°C are suitable. For plasma polymerization typically temperatures in the range of about 20°C to about 100°C may be employed.

The fluorocarbon polymer may also be formed in situ at the can walls using plasma polymerization of the fluorocarbon monomers. Fluorocarbon polymer film

may be blown inside the MDI cans to form bags. A variety of fluorocarbon polymers such as ETFE, FEP, and PTFE are available as film stock.

The MDI's taught herein may be prepared by methods of the art (e.g., see Byron, above and U.S. patent 5,345,980) substituting conventional cans for those coated with a fluorinated polymer. That is, beclomethasone dipropionate and other components of the formulation are filled into an aerosol can coated with a fluorinated polymer. The can is fitted with a cap assembly which is crimped in place. The suspension of the drug in the fluorocarbon propellant in liquid form may be introduced through the metering valve as taught in U.S. 5,345,980 incorporated herein by reference.

The MDI's with fluorocarbon coated interiors taught herein may be used in medical practice in a similar manner as non-coated MDI's now in clinical use. However the MDI's taught herein are particularly useful for containing and dispensing inhaled drug formulations with hydrofluoroalkane fluorocarbon propellants such as 134a with little, or essentially no, excipient and which tend to deposit or cling to the interior walls and parts of the MDI system. In certain case it is advantageous to dispense an inhalation drug with essentially no excipient, e.g., where the patient may be allergic to an excipient or the drug reacts with an excipient.

MDI's containing the formulations described hereinabove, MDI systems and the use of such MDI systems for the treatment of respiratory disorders e.g. asthma comprise further aspects of the present invention.

It will be apparent to those skilled in the art that modifications to the invention described herein can readily be made without departing from the spirit of the invention. Protection is sought for all the subject matter described herein including any such modifications.

The following non-limitative Examples serve to illustrate the invention.

EXAMPLES

Example 1

Standard 12.5 mL MDI cans (Presspart Inc., Cary, NC) were spray-coated (Livingstone Coatings, Charlotte, NC) with primer (DuPont 851-204) and cured to the vendor's standard procedure, then further spray-coated with either FEP or PFA (DuPont 856-200 and 857-200, respectively) and cured according to the vendor's standard procedure. The thickness of the coating is approximately 10μm to 50μm. These cans are then purged of air (see PCT application number W094/22722 (PCT/EP94/00921)), the valves crimped in place, and a suspension of about 24 mg beclomethasone dipropionate in about 18 gm P134a is filled through the valve.

Example 2

Standard 0.46 mm thick aluminum sheet (United Aluminum) was spray-coated (DuPont, Wilmington, DE) with FEP (DuPont 856-200) and cured. This sheet was then deep-drawn into cans (Presspart Inc., Cary, NC). The thickness of the coating is approximately 10μm to 50μm. These cans are then purged of air, the valves crimped in place, and a suspension of about 60 mg beclomethasone dipropionate in about 18 gm P134A is filled through the valve.

Example 3

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

Example 4

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

Example 5

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

Example 6

Standard 0.46mm thick aluminium sheet is spray coated with FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

Example 7

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans

are then purged of air, the valves crimped in place, and a suspension of about 68mg micronised beclomethasone dipropionate monohydrate in about 6.1mg water and about 18.2g P134a is filled through the valve.

Example 8

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

Example 9

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

Example 10

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

Example 11

Standard 0.46mm thick aluminium sheet is spray coated with FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

Example 12

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 68mg micronised beclomethasone dipropionate monohydrate in about 182mg ethanol and about 18.2g P134a is filled through the valve.

Example 13

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-PES blend (DuPont) as a single coat and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

Example 14

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with PTFE-FEP-polyamideimide blend (DuPont) and cured according to the vendor's standard procedure. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

Example 15

Standard 12.5ml MDI cans (Presspart Inc., Cary NC) are spray-coated with FEP powder (DuPont FEP 532) using an electrostatic gun. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

Example 16

Standard 0.46mm thick aluminium sheet is spray coated with FEP-Benzoguanamine and cured. This sheet is then deep-drawn into cans. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

Example 17

Standard 12.5 ml MDI cans (Presspart Inc., Cary NC) are spray-coated with an aqueous dispersion of PFA (Hoechst PFA-6900n) and cured. The thickness of the coating is between approximately 1μm and approximately 20μm. These cans are then purged of air, the valves crimped in place, and about 13.6mg micronised beclomethasone dipropionate in about 107mg ethanol and about 21.4g P227 is filled through the valve.

Examples 18-22

Examples 3 to 7 are repeated except that about 24mg salbutamol as the free base or equivalent weight of salt e.g. sulphate with about 12mg beclomethasone dipropionate monohydrate in about 364mg ethanol and about 18.2g P134a is filled through the valve.

Examples 23-42

Examples 3 to 22 are repeated except that modified 12.5ml MDI cans having a substantially ellipsoidal base (Presspart Inc., Cary NC) are used.

Dose delivery from the MDIs tested under simulated use conditions is found to be constant, compared to control MDIs filled into uncoated cans which exhibit a significant decrease in dose delivered through use.

We claim:

1. A metered dose Inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising beclomethasone dipropionate or a physiologically acceptable solvate thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

2. An inhaler according to Claim 1 containing said drug formulation.

3. An inhaler according to Claim 2 wherein said drug formulation further comprises a surfactant.

4. An inhaler according to Claim 2 or Claim 3 wherein said drug formulation further comprises a polar cosolvent.

5. An inhaler according to claim 2 wherein said drug formulation comprises 0.01 to 5 % w/w based on the weight of propellant of a polar cosolvent, which formulation is substantially free of surfactant.

6. An inhaler according to Claim 4 or Claim 5, wherein the polar cosolvent is ethanol.

7. An inhaler according to any one of Claims 2 to 6, wherein said drug formulation comprises beclomethasone dipropionate or a physiologically acceptable solvate thereof in combination with salmeterol or salbutamol or a physiologically acceptable salt thereof.

8. An inhaler according to Claim 2, wherein said drug formulation comprises

(a) beclomethasone dipropionate monohydrate, the particle size of substantially all the monohydrate being less than 20 microns;

(b) at least 0.15% by weight of the formulation of water in addition to the water of crystallisation associated with the monohydrate; and

(c) a fluorocarbon propellant.

9. An inhaler according to Claim 8, wherein the formulation further comprises 0.05 to 3% w/w based on the propellant of a polar cosolvent.

10. An inhaler according to Claim 9, wherein the polar cosolvent is ethanol.

11. An inhaler according to Claim 2, wherein said drug formulation consists essentially of beclomethasone dipropionate or a physiologically acceptable solvate thereof, optionally in combination with one or more other pharmacologically active agents, a fluorocarbon propellant and 0.01 to 5 % w/w based on the propellant of a polar cosolvent, which formulation is substantially free of surfactant.

12. An inhaler according to any one of Claims 2 to 11, wherein the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof.

13. An inhaler according to Claim 12, wherein the fluorocarbon propellant is 1,1,1,2-tetrafluoroethane.

14. An inhaler according to any one of claims 1 to 13 comprising a can made of metal wherein part or all of the internal metallic surfaces are coated.

15. An inhaler according to Claim 14 wherein the metal is aluminium or an alloy thereof.

16. An inhaler according to any one of Claims 1 to 15, wherein said fluorocarbon polymer is a perfluorocarbon polymer.

17. An inhaler according to Claim 16 wherein said fluorocarbon polymer is selected from PTFE, PFA, FEP and mixtures thereof.

18. An inhaler according to any one of Claims 1 to 17, wherein said fluorocarbon polymer is in combination with a non-fluorocarbon polymer selected from polyamideimide and polyethersulphone.

19. An inhaler according to any one of Claims 1 to 18 comprising a substantially ellipsoidal base.

20. A metered dose inhaler system comprising a metered dose inhaler according to any one of Claim 1 to 19 fitted into suitable channelling device for oral or nasal inhalation of the drug formulation.

21. Use of a metered dose inhaler system according to Claim 20 for the treatment of respiratory disorders.

ABSTRACT

A metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising beclomethasone dipropionate or a physiologically acceptable solvate thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

COMBINED DECLARATION FOR P ENT APPLICATION AND POWER OF A ORNEY
(Includes Reference to PCT International Applicat.)

ATTORNEY'S DOCKET NUMBER
GI2180USW

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

the specification of which (check only one item below):

[ ]is attached hereto with Preliminary Amendment.

[X] was filed as United States application Serial No. 08/945,141 on October 14, 1997 and was amended on September 21, 1998 and September 28, 1998 (if applicable)
[X] was filed as PCT international application Number PCT/US96/05009 on April 11, 1996

and was amended under PCT Article 19 on _____(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 and all information which became available between the filing of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under Title 35, United States Code. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) having a filing date before that of the application(s) on which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
1.PCT	PCT/US96/05009	11 April 1996	X
2.			
3.			
4.			
5.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No..	Filing Date (MM/DD/YYYY)	
1.		
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4.		
5.		

COMBINED DECLARATION FOR P. ENT APPLICATION AND POWER OF ATTORNEY (Continued - Includes References to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: **GI2180USW**

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or §365(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
08/422,280	April 14, 1995			X

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S.FILING NUMBERS ASSIGNED (if any)			
PCT/US96/05009	April 11, 1996			X	

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number)

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Robert H. Brink	Reg. No. 36,094	Shah R. Makujina	Reg. No. 41,174	
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2 0 1	FULL NAME OF INVENTOR	FAMILY NAME: **BRITTO**	FIRST GIVEN NAME: **Ignatius**	SECOND GIVEN NAME/INITIAL: **Loy**
	RESIDENCE & CITIZENSHIP	CITY: **Cary**	STATE OR FOREIGN COUNTRY: **NC**	COUNTRY OF CITIZENSHIP: **US**
	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **Glaxo Wellcome Inc.** **Five Moore Drive, PO Box 13398**	CITY: **RTP**	STATE & ZIP CODE/COUNTRY: **NC 27709-3398, US**
2 0 2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2 0 3	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2 0 4	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2 0 5	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

COMBINED DECLARATION FOR P. ENT APPLICATION AND POWER OF A. ORNEY (Continued - Includes References to PCT International Applications)	ATTORNEY'S DOCKET NUMBER GI2180USW

2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
6	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
7	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
8	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
9	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
1	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
0	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201 / Ignacius Britto.	Signature of Inventor 202	Signature of Inventor 203
Date 7th, Jan, 1999	Date	Date
Signature of Inventor 204	Signature of Inventor 205	Signature of Inventor 206
Date	Date	Date
Signature of Inventor 207	Signature of Inventor 208	Signature of Inventor 209
Date	Date	Date
Signature of Inventor 210		
Date		

Supplemental Declaration

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER GI2180USW

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

the specification of which (check only one item below):

[ ]is attached hereto with Preliminary Amendment.

[X] was filed as United States application Serial No. 08/945,141 on 14 October 1997 and was amended on _____(if applicable).

[X] was filed as PCT international application Number PCT/US96/05009 on 11 April 1996

and was amended under PCT Article 19 on _____(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 and all information which became available between the filing of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under Title 35, United States Code. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) having a filing date before that of the application(s) on which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
1.**PCT**	**PCT/US96/05009**	**11 April 1996**	
2.			
3.			
4.			
5.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No..	Filing Date (MM/DD/YYYY)	
1.		
2.		
3.		
4.		
5.		

Supplemental Declaration

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued - Includes References to PCT International Applications)

ATTORNEY'S DOCKET NUMBER: **GI2180USW**

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or §365(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
08/422,280	April 14, 1995			X

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S.FILING NUMBERS ASSIGNED (if any)			
PCT/US96/05009	April 11, 1996				X

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number)

David J. Levy	Reg. No. 27,655	James P. Riek	Reg. No. 39,009	Gerald M. Murphy, Jr. Reg. No. 28,977
Charles E. Dadswell	Reg. No. 35,851	Robert T. Hrubiec	Reg. No. 36,392	
Karen L. Prus	Reg. No. 39,337	Frank P.Grassler	Reg No. 31,164	
Robert H. Brink	Reg. No. 36,094	Shah R. Makujina	Reg. No. 41,174	

Send Correspondence to:
David J. Levy, Patent Counsel
Global Intellectual Property Department
Glaxo Wellcome Inc.
Five Moore Drive, PO Box 13398
Research Triangle Park, NC 27709

Direct Telephone Calls to:
Gerald M. Murphy, Jr.
(703) 205-8000

2	FULL NAME OF INVENTOR	FAMILY NAME: **ASHURST**	FIRST GIVEN NAME: **Ian**	SECOND GIVEN NAME/INITIAL: **Car;**
0	RESIDENCE & CITIZENSHIP	CITY: **Ware**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
1	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **Glaxo Wellcome Inc. Five Moore Drive, PO Box 13398**	CITY: **RTP**	STATE & ZIP CODE/COUNTRY: **NC 27709, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **HERMAN**	FIRST GIVEN NAME: **Craig**	SECOND GIVEN NAME/INITIAL: **Steven**
0	RESIDENCE & CITIZENSHIP	CITY: **Raleigh**	STATE OR FOREIGN COUNTRY: **NC**	COUNTRY OF CITIZENSHIP: **US**
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2	FULL NAME OF INVENTOR	FAMILY NAME: **LI-BOVET**	FIRST GIVEN NAME: **Li**	SECOND GIVEN NAME/INITIAL:
0	RESIDENCE & CITIZENSHIP	CITY: **Scotch Plains**	STATE OR FOREIGN COUNTRY: **NJ**	COUNTRY OF CITIZENSHIP: **CH**
3	POST OFFICE ADDRESS	POST OFFICE ADDRESS: **172 Spruce Mill Lane**	CITY: **Scotch Plains**	STATE & ZIP CODE/COUNTRY: **NJ 07076, US**
2	FULL NAME OF INVENTOR	FAMILY NAME: **RIEBE**	FIRST GIVEN NAME: **Michael**	SECOND GIVEN NAME/INITIAL: **Thomas**
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2	FULL NAME OF INVENTOR	FAMILY NAME:	FIRST GIVEN NAME:	SECOND GIVEN NAME/INITIAL:
0	RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS:	CITY:	STATE & ZIP CODE/COUNTRY:

Supplemental Declaration

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued - Includes References to PCT International Applications)	ATTORNEY'S DOCKET NUMBER GI2180USW

206	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
207	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
208	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
209	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
210	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201	Signature of Inventor 202	Signature of Inventor 203
Date	Date	Date
	X 04 March 1998	
Signature of Inventor 204	Signature of Inventor 205	Signature of Inventor 206
X		
Date	Date	Date
X 04 Mar 98		
Signature of Inventor 207	Signature of Inventor 208	Signature of Inventor 209
Date	Date	Date
Signature of Inventor 210		
Date		

Supplemental Declaration

CLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY
(to PCT International Applications)

ATTORNEY'S DOCKET NUMBER
GI2180USW

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

the specification of which (check only one item below):

[ ]is attached hereto with Preliminary Amendment.

[X] was filed as United States application Serial No. 08/945,141 on 14 October 1997 and was amended on _____(if applicable).

[X] was filed as PCT international application Number PCT/US96/05009 on 11 April 1996

and was amended under PCT Article 19 on _____(if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 and all information which became available between the filing of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under Title 35, United States Code. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) having a filing date before that of the application(s) on which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
1.**PCT**	**PCT/US96/05009**	**11 April 1996**	
2.			
3.			
4.			
5.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No..	Filing Date (MM/DD/YYYY)	
1.		
2.		
3.		
4.		
5.		

Supplemental Declaration

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued - Includes References to PCT International Applications)	ATTORNEY'S DOCKET NUMBER GI2180USW

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or §365(c) of any PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
08/422,280	April 14, 1995			X

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S.FILING NUMBERS ASSIGNED (if any)			
PCT/US96/05009	April 11, 1996				X

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David J. Levy	Reg. No. 27,655	James P. Riek	Reg. No. 39,009	Gerald M. Murphy, Jr. Reg. No. 28,977
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Karen L. Prus	Reg. No. 39,337	Frank P.Grassler	Reg. No. 31,164	
Robert H. Brink	Reg. No. 36,094	Shah R. Makujina	Reg. No. 41,174	

Send Correspondence to:	Direct Telephone Calls to:
David J. Levy, Patent Counsel **Global Intellectual Property Department** **Glaxo Wellcome Inc.** **Five Moore Drive, PO Box 13398** **Research Triangle Park, NC 27709**	Gerald M. Murphy, Jr. (703) 205-8000

2	FULL NAME OF INVENTOR	FAMILY NAME: **ASHURST**	FIRST GIVEN NAME: **Ian**	SECOND GIVEN NAME/INITIAL: **Car;**
0	RESIDENCE & CITIZENSHIP	CITY: **Ware**	STATE OR FOREIGN COUNTRY: **GB**	COUNTRY OF CITIZENSHIP: **GB**
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0	RESIDENCE & CITIZENSHIP	CITY: **Raleigh**	STATE OR FOREIGN COUNTRY: **NC**	COUNTRY OF CITIZENSHIP: **US**
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0	RESIDENCE & CITIZENSHIP	CITY:	STATE OR FOREIGN COUNTRY:	COUNTRY OF CITIZENSHIP:
5	POST OFFICE ADDRESS	POST OFFICE ADDRESS:	CITY:	STATE & ZIP CODE/COUNTRY:

Supplemental Declaration

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued - Includes References to PCT International Applications)	ATTORNEY'S DOCKET NUMBER GI2180USW

202	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
206	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY NC	COUNTRY OF CITIZENSHIP US
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
207	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
207	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
208	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
208	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
209	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
209	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
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210	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
211	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 201 J Gail	Signature of Inventor 202	Signature of Inventor 203
Date 5th March 1998	Date	Date
Signature of Inventor 204	Signature of Inventor 205	Signature of Inventor 206
Date	Date	Date
Signature of Inventor 207	Signature of Inventor 208	Signature of Inventor 209
Date	Date	Date
Signature of Inventor 210		
Date		

Supplemental Declaration

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to PCT International Applications)	ATTORNEY'S DOCKET NUMBER GI2180USW

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METERED DOSE INHALER FOR BECLOMETHASONE DIPROPIONATE

the specification of which (check only one item below):

[ ] is attached hereto with Preliminary Amendment.

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PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

COUNTRY (if PCT indicate PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
1.PCT	**PCT/US96/05009**	**11 April 1996**	
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3.			
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I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No..	Filing Date (MM/DD/YYYY)	
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U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
08/422,280	April 14, 1995			X

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Supplemental Declaration

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Continued - Includes References to PCT International Applications)	ATTORNEY'S DOCKET NUMBER GI2180USW

2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY NC	COUNTRY OF CITIZENSHIP US
6	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
7	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
0	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
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2	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME/INITIAL
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9	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY
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Date	Date	Date X 3/6/98
Signature of Inventor 204	Signature of Inventor 205	Signature of Inventor 206
Date	Date	Date
Signature of Inventor 207	Signature of Inventor 208	Signature of Inventor 209
Date	Date	Date
Signature of Inventor 210		
Date		